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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,359	CHABOT ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,28,85-87,104,107-109,116,117,123,130,131 and 138-148* is/are pending in the application.

4a) Of the above claim(s) *85-87,104,107-109,116,117,123,130,131 and 138-148* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-14-05, 9-14-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

CFR §1.821(d) reads as follows:

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

It is found that Figures 4A and 5A contain nucleic acid sequences that are not preceded by appropriate SEQ ID NOs. Applicant is required to amend the Figures or the description of the drawings accordingly. See the attached Notice to Comply.

Election/Restrictions

Applicant's election with traverse of claims 1-7 and 28 and SEQ ID NO:12 in the reply filed on December 31, 2007 is acknowledged. The traversal is on the ground(s) that there is no serious search burden to examine all pending claims. This is not found persuasive because the

issue of search burden was neither addressed nor argued in the restriction requirement because the claims were restricted under PCT Rules 13.1 and 13.2. Note that this application is filed under 35 U.S.C. 371 and 37 CFR 1.495.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Currently, claims 1-7, 28, 85-87, 104, 107-109, 116-117, 123, 130-131, and 138-148 are pending. Claims 85-87, 104, 107-109, 116-117, 123, 130-131, and 138-148 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 1-7 and 28 are currently under examination on the merits in the instant case.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/402,765, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The disclosure of 60/402,765 fails to provide adequate support for the claimed SEQ ID NO:12 of claim 28. Further, it also fails to provide adequate enablement for the claimed method performed in a cell in a patient as claimed in claim 7. Accordingly, the benefit of a prior filing date for claims 7 and 28 is denied and therefore the earliest filing date for claims 7 and 28 will be June 30, 2003. If applicant believes that 60/402,765 provides adequate support and enablement for the claimed subject matter in claims 7 and 28, applicant is advised to point out the particulars in response to this Office action.

Specification

The disclosure is objected to because of the following informalities:

1) The specification contains sequence rule-noncompliant subject matter. See page 2 of this Office action.

2) The instant specification contains erroneous or inconsistent information on page 19. The disclosure on page 19 states, "Figs. 5A-E illustrate splicing interference mediated by the protein-binding antisense oligo *in vivo*." However, the detailed description that continues into page 20 clearly shows that the data illustrated in Figures 5A-E are not *in vivo*, but *in vitro* data as the experiments were performed in cultured cells and the antisense oligos were "transfected".

Appropriate correction/clarification is required.

Claim Objections

Claim 28 is objected to for containing non-elected SEQ ID NOs. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is drawn to a method wherein protein binding is "effected" prior to hybridizing an oligonucleotide. The literal meaning of the word "effect" is "to cause to come into being" or "accomplish" or "put into operation" or "perform". See for example the Merriam-Webster dictionary. With regard to the claimed method, the instant specification does not provide any clear definition as to what is meant by the claimed method step of "effecting" protein binding. Since it is unclear how to interpret the undefined term "effect" within the context of the claim, and since the specification is completely silent about the claimed method step (e.g., how to achieve "effecting" said binding), it is concluded that one of ordinary skill in the art would not be able to ascertain the metes and bounds encompassed by the claimed method step in claim 2. Further, claim 2 claims that the binding step is effected prior to the hybridizing step "or

thereafter". Since there is no recited method step other than the step of hybridizing, it is unclear what other steps are meant to be embraced by the language "thereafter".

Claim 28 recites the limitation "said oligonucleotide moiety" in line 1. There is insufficient antecedent basis for this limitation in the claim, because claim 1 does not recite "oligonucleotide moiety".

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating splicing site selection in a cell *in vitro*, does not reasonably provide enablement for the method performed in a cell *in vivo* or in a cell that is in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient

evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims embrace both *in vitro* and *in vivo* methods for modulating splice site selection of a target gene by introducing an oligonucleotide that binds to a protein moiety, as evidenced by the disclosure of the specification that teaches the methods of the present invention are "useful as *in vitro* or *in vivo* tools to examine splicing in human or animal genes" (see page 33) and claim language of claim 7, which specifically recites that the cell "is in a patient".

The unpredictability of delivering oligonucleotides into target cells *in vivo* was widely accepted in the art as of the earliest filing date sought in the instant application. The contributing factors to such *in vivo* administration include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic or inhibitory effect. See for example Opalinska et al. (*Nature Reviews Drug Discovery*, 1:503-514, 2002), in which they teach that "It is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA...Another problem in this field is the limited ability to deliver nucleic acids into cells and

have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient." See page 511.

Given this unpredictability with regard to *in vivo* behavior of oligonucleotides, a person of ordinary skill in the art would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant modulation of targeted pre-mRNA splicing, as claimed. The specification provides only *in vitro* examples wherein transfected oligonucleotides interfere with splicing in cultured cells. However, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of splicing of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of modulating splicing of any target gene in any organism as the art of introducing antisense oligonucleotides into an organism is neither routine nor predictable. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-7 and 28 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Newman et al. (US 2002/0068321 A1).

The claims are drawn to methods of repressing pre-mRNA splicing by hybridizing an oligonucleotide conjugated to a protein-binding moiety, in a mammalian cell *in vitro*, wherein the oligonucleotide comprises a nucleic acid sequence complementary to a specific region upstream of a splice site in a target pre-mRNA, wherein the splice site is a 5' splice site, a 3' splice site.

Newman et al. teach a method of modulating RNA splicing and RNA splice site selection in cells *in vitro* by using a polynucleotide that is complementary to hnRNP A1 to block the activity of hnRNP A1, which promotes alterative splicing and splice site selection (paragraphs 0364-0380, 0389, 0392-0395; Examples 1 and 2). They teach that hnRNP A1 is known to play a role in splicing pre-mRNAs and RNA splice site selection, wherein hnRNP A1 is highly conserved in mammals (paragraphs 0308, 0318). They teach that hnRNP A1 promotes RNA-RNA strand annealing and therefore it activates antisense regulatory mechanisms (paragraphs 0312, 0339). Further, they teach that hnRNP A1 recognizes a highly conserved, consensus sequence of "UAGGGA/U" and that hnRNP A1 modulates splice site selection or alternative splicing by binding to sequences containing "UAGGGA/U" (paragraph 0337). They teach that that the consensus sequence is found in the 5' and 3' splice sites in vertebrate pre-mRNAs (paragraph 0340). Furthermore, they teach that the ability of hnRNP A1 to bind to the consensus sequence increases if the consensus sequence is duplicated and separated by two nucleotides (paragraph 0340). They teach that alternative splicing involves alternative 5' or 3' splice sites (paragraph 0334). Accordingly, all claim limitations are taught by Newman et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newman et al. (US 2002/0068321 A1) as applied to claims 1-6 above, further in view of Taylor et al. (*Nature Biotechnology,* 1999, 17:1097-1100, applicant's citation).

The claims are drawn to methods of repressing pre-mRNA splicing by hybridizing an oligonucleotide conjugated to a protein-binding moiety, in a mammalian cell *in vitro*, wherein the oligonucleotide comprises a nucleic acid sequence complementary to a specific region upstream of a splice site in a target pre-mRNA, wherein the splice site is a 5' splice site, a 3' splice site, wherein the oligonucleotide is SEQ ID NO:12, which is targeted to the pre-mRNA of Bcl-x (see page 12 of the specification).

Newman et al. teach a method of modulating RNA splicing and RNA splice site selection in cells *in vitro* by using a polynucleotide that is complementary to hnRNP A1 to block the activity of hnRNP A1, which promotes alterative splicing and splice site selection (paragraphs 0364-0380, 0389, 0392-0395; Examples 1 and 2). They teach that hnRNP A1 is known to play a role in splicing pre-mRNAs and RNA splice site selection, wherein hnRNP A1 is highly conserved in mammals (paragraphs 0308, 0318). They teach that hnRNP A1 promotes RNA-

RNA strand annealing and therefore it activates antisense regulatory mechanisms (paragraphs 0312, 0339). Further, they teach that hnRNP A1 recognizes a highly conserved, consensus sequence of "UAGGGA/U" and that hnRNP A1 modulates splice site selection or alternative splicing by binding to sequences containing "UAGGGA/U" (paragraph 0337). They teach that that the consensus sequence is found in the 5' and 3' splice sites in vertebrate pre-mRNAs (paragraph 0340). Furthermore, they teach that the ability of hnRNP A1 to bind to the consensus sequence increases if the consensus sequence is duplicated and separated by two nucleotides (paragraph 0340). They teach that alternative splicing involves alternative 5' or 3' splice sites (paragraph 0334). Newman et al. do not teach targeting Bcl-x pre-mRNA.

Taylor et al. teach a method of modulating Bcl-x pre-mRNA splicing by antisense oligonucleotides in cultured human cells *in vitro,* wherein the modulating step produces increased Bcl-xS expression while reducing the production of Bcl-xL. They teach that alternative splicing of the Bcl-x pre-mRNA produces either Bcl-xL (pro-survival, anti-apoptotic) or Bcl-xS (pro-apoptotic). Given the two functionally different mRNA products of Bcl-x pre-mRNA by alternative splicing, they teach that reducing the production of Bcl-xL but increasing the production of Bcl-xS could be developed into a valuable anticancer methodology. See page 1097. They teach that their method of modulating the Bcl-x pre-mRNA slice site selection comprises the method of inhibiting the use of the 5' splice site in exon 2 of the Bcl-xL RNA by using an antisense oligonucleotide that hybridizes to the Bcl-x pre-mRNA 15 nucleotides upstream of the Bcl-xL splice donor site. See pages 1097-1099. They teach that modulating Bcl-x expression levels or expression of alternatively spliced genes by using antisense

oligonucleotides that control splice site selection may be valuable in regulating cell survival. See pages 1099-1100.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the *in vitro* method of using a polynucleotide that is complementary to hnRNP A1 to block the activity of hnRNP A1 of Newman et al. with that of using a polynucleotide that is complementary to 5' splice site of the Bcl-x pre-mRNA.

One of ordinary skill in the art would have been motivated to combine the teachings of the prior art, with a reasonable expectation of success, because the use of RNP A1 binding sequences known as "UAGGGA/U", especially by duplicating them separated by two nucleotides, were known to be effective in modulating splicing pre-mRNAs and RNA splice site selection as taught by Newman et al., and since the use of antisense oligonucleotides hybridizing to the Bcl-x pre-mRNA was known to be effective in modulating splice site selection as taught by Taylor et al. That is, since Taylor et al. taught modulating alternative splicing of the Bcl-x pre-mRNA is critical in regulating cell survival (production of Bcl-xL) or cell apoptosis (production of Bcl-xS), and since Newman et al. taught hnRNP A1 modulates splice site selection or alternative splicing by binding to sequences containing "UAGGGA/U", one of ordinary skill in the art would have been motivated to combine the two antisense sequences to help facilitate or promote effective splice site selection of the Bcl-x pre-mRNA, thereby controlling cell fate, either survival or death. Since the consensus RNP A1 binding sequences were known, and furthermore since the sequence of the known Bcl-x pre-mRNA has those consensus RNP A1 binding sequences in its crucial splice site (which determines cell death for Bcl-xS or cell survival for Bcl-xL), it would have been *prima facie* obvious to design the

oligonucleotides that could be used to target each of the splice sites in the Bcl-x pre-mRNA, including SEQ ID NO: 12, with a reasonable expectation of success. Further, since Newman et al. expressly taught that hnRNP A1 promotes RNA-RNA strand annealing and therefore it activates antisense regulatory mechanisms (paragraphs 0312, 0339), the skilled artisan would have been further motivated to conjugate the antisense sequence comprising "UAGGGA" and "UAGGGU" separated by two nucleotides as directed by Newman et al. for greater binding efficiency of hnRNP A1 (see paragraph 0340), thereby increasing the annealing affinity as well as the antisense mechanism of the anti-Bcl-x antisense oligonucleotide of Taylor et al.

See also *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Since both antisense oligonucleotide hybridizing to an upstream of the Bcl-xL splice donor site in the Bcl-x pre-mRNA and the oligonucleotide comprising two highly conserved, consensus sequences of "UAGGGA" and "UAGGGU" were recognized in the art as agents that modulate splice site selection, it would have been *prima facie* obvious to combine them for modulating alternative splicing/splice site selection with a reasonable expectation of success. See also MPEP 2144.06.

Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J E Angell/
Primary Examiner

Oligonucleotide	Target	Binding site sequence	Complementary region sequence
X-M4A1	Bcl-x	TTTTTGATAGGGAAAT (SEQ ID NO:11) hnRNP A1 binding site	GCCGCCGUUCUCCUGGAUC C (SEQ ID NO:10) -4 to -23 proximal 5' splice site
X-M4A1W	Bcl-x	UAUGAUAGGGACUUAGG GUG (SEQ ID NO:12) hnRNP A1 binding site	GCCGCCGUUCUCCUGGAUC C (SEQ ID NO:10) -4 to -23 proximal 5' splice site
X-M4A1M	Bcl-x	UAUGAUACGCACUUACG CUG (SEQ ID NO:13) *mutated hnRNP A1 binding sites*	GCCGCCGUUCUCCUGGAUC C (SEQ ID NO:10) *-4 to -23 proximal 5' splice site*
C-RNA	AAUGUCUGCUACUGGAAG (SEQ ID NO: 14) *control RNA sequence*		

While the first aspect of the invention makes use of hybrid oligo that interferes with splice site recognition because the hybrid oligo hybridizes close to the splice site, the second aspect of the invention features a method to alter splice site use by using hybrid oligos hybridizing at a greater distance from the splice sites. In this second aspect, we are using hybrid oligos that are bound by hnRNP A1/A2 proteins to influence alternative splicing and the splicing of long introns by a mechanism that involves looping out the sequences between the sites bound by the oligos. Providing A1/A2 through the use of hybrid oligos can therefore position A1/A2 to act on the splicing of large introns and on alternative splicing.

In an alternative embodiment of the present invention, the extension is attached to an other oligo or a secondary structure of the oligonucleotide, to form a binding site for a protein which bound to double-stranded RNA.

For the purpose of the present invention, the following abbreviations and terms are defined below.

The term "3' splice site" is intended to mean pre-mRNA sequences at the 3' intron/exon boundary which generally contains the sequence YnCAG/ (where / is the intron exon boundary, Y=pyrimidines

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 37 CFR §1.821(g). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. §1.821(c).
- [ ] 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. §1.821(e).
- [ ] 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. §1.822 and/or 1.823, as indicated on the attached copy of the marked-up Raw Sequence Listing.
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. §1.825(d).
- [ ] 6. The paper copy of the Sequence Listing is not the same as the computer readable from of the Sequence Listing as required by 37 C.F.R. §1.821(e).
- [X] 7. Other: Figures 4A and 5A contain nucleotide sequences that do not comply with the requirements indicated above.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the Sequence Listing. (If the unidentified sequences are not provided on the CRF)
- [X] An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)
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